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Review Article

An Update to the Current Passive Immunotherapeutic Approaches to COVID-19 Treatment

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Abstract

The newest member of the coronavirus family, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has caused a pandemic (after being endemic in Wuhan, China) and is threatening to the health of every person on the planet. Nearly 1.5 years after the coronavirus disease 2019 (COVID-19) worldwide challenges, a gold-standard, highly effective anti-viral therapy is still undiscovered. The urgency of this pandemic has forced all scientists to tackle this problem using any logical mode of therapy. One such approach is modulating and manipulating the host's immune response using immunotherapy against SARS-CoV-2 infection and its collateral complications. This review article aims to present an update on the immunopathogenesis of SARS-CoV-2, and how it, directly and indirectly, deteriorates the patients' condition. The latest findings of preclinical and clinical trials using passive immunotherapy in the context of the COVID-19 are compiled as well.

Keywords: Immunotherapy; SARS-CoV-2; COVID-19; Adoptive Immunotherapy

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Introduction

December 2019, marks one of the most important time periods in the history of mankind with the inception of a contagious Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for a pandemic disease, later called the Coronavirus Disease 2019 (COVID-19). Naturally, finding a treatment for this disease became the priority of scientists worldwide. Immunotherapy, which uses the immune system in the fight against the disease, has been rapidly growing as a translational science (1). Convalescent plasma therapy, cell therapy, cytokine therapy, pooled antibodies, and monoclonal antibodies are some of the potential treatments offered by immunotherapy, as stand-alone or combination therapies, whose safety and efficacy are being probed in preclinical and clinical studies (2). These passive immunotherapies endow the patients with already available treatments to repel SARS-CoV-2 infection. This is especially crucial in people who suffer from immunodeficiency disorders or patients on immunosuppressive drugs who are unable to take advantage of vaccines (3).

Although vaccines, as a form of active immunotherapy, have been successful in reducing the burden, mortality and morbidity of the disease, no stone must be left unturned in finding a standard treatment for COVID-19. Therefore, understanding the immunopathogenesis of COVID-19, and the interaction of immune cells with SARS-CoV-2, also, are necessary aspects of achieving a curative treatment (4). Here, we gathered an overview of the structure and functions of SARS-CoV-2, and the responses elicited from the innate and adaptive immunities, following invasion of the virus. Compiled and reviewed were the recent advances of the most distinguished passive immunotherapeutic approaches for the treatment of COVID-19. Generally, the immunotherapeutic methods aim to either inhibit the infection of SARS-CoV-2 and its spread, to modify the immune response, or to ameliorate the side effects associated with overzealous activation of the immune system (5).

A Brief Overview of SARS-CoV-2 Structure and Pathogenesis

SARS-CoV-2 is a positive sense, single-stranded ribonucleic acid (ssRNA) virus, enveloped in nucleocapsid phosphoproteins and belongs to the *Betacoronavirus* genus and the *Coronaviridae* family. This is not the first time that a *betacoronavirus* has threatened humanity, as previously, SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV zoonotic pathogens, have been endemic. The genome of SARS-CoV-2, which is 29,881 np long, has 80% homology to SARS-CoV, and with 96.2% homology to bat RaTGI3 virus, hence it is assumed that bats are the origin of this emerging virus (6). The 3' end of the genomes encodes four prominent structural proteins: the Spike (S) protein, the Membrane (M) protein, the Envelope (E) protein, and the Nucleocapsid (N) protein (**Figure 1**). The genome encodes 9860 amino

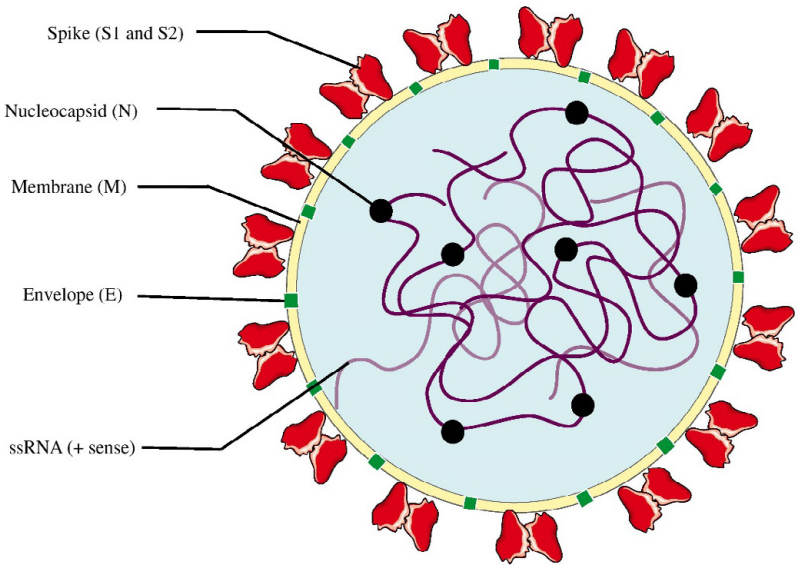

Figure 1. A schematic depiction of SARS-CoV-2 virus.

acids in total, 1273 of which are S proteins. The S1 subunit (residue 14-685) of spike glycoprotein (having four core domains of $S1_A$ to $S1_D$) has the receptor-binding domain (RBD) (residue 319-541) that binds to the angiotensin-converting enzyme II (ACE2) of the host cell, while the S2 subunit (residue 686-1273) facilitates the fusion of the virus to the cell membrane. The cleavage of the S protein into its subunits is undertaken by host proteases, including transmembrane protease serine 2 (TMPRSS2), allowing the endocytosis of the virus (7). Thus, any cell expressing the ACE-2 receptor, such as type I pneumocytes, type II alveolar epithelial cells, and the cells of small intestines, heart, and kidneys are a potential target for SARS-CoV-2. This is the basis for many cases of multiple organ failure in COVID-19 patients (8).

SARS-CoV-2 is transmitted via tiny droplets from infected patients, and its pathophysiology is quite similar to that of SARS-CoV. The median incubation time of the virus is 5.1 days, and 97.5% of the affected populace, develop symptoms within 11.5 days, which includes dry cough, fever, and dyspnea with headache, joint and muscle pain, fatigue, and gastrointestinal issues (9). The virus mainly disrupts the respiratory system, and the symptoms may range from mild to severe, such as acute respiratory distress syndrome (ARDS) accompanied by hyperinflammation, depending on the patients' age and the dysregulation of the immune system (10). Diagnosis of the infection can be confirmed via chest computed tomography (CT) scan showing an opaque ground-glass view in tandem with molecular tests, particularly real-time reverse transcription-polymerase chain reaction (qRT-PCR) test.

The Immunopathogenesis of SARS-CoV-2

SARS-CoV-2 exerts its cytopathic effects by invading and destroying ACE2-expressing cells as a part of its replication cycle (11). The recognition of the main damage-associated molecular patterns (DAMP) and the viral pathogen-associated molecular patterns (PAMP) markers by pattern recognition receptors (PRRs), elicits a response from innate immunity. Three initial responses are key in limiting the virus invasion: (1) maturation and induction of antigen-presenting cells (APCs), especially through dendritic cells (DCs); (2) synthesis of type I interferons (IFNs); (3) secretion of inflammatory cytokines (12). The pyroptosis of alveolar cells, triggers the release of interleukin-1β (IL-1β) and IL-18 pro-inflammatory cytokines, which in turn, recruit macrophages/monocytes and neutrophils to the infection site. Besides other functions, the recruited cells also secrete inflammatory cytokines, such as IL-6, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1-α (MIP1-α), MIP1-1β, and monocyte chemoattractant protein-1 (MCP-1), to further recruit the immune cells from the blood circulation. Thus, elevation of inflammatory cytokines and markers of systemic inflammation, such as C-reactive proteins (CRP), d-dimer, and ferritin, are the hallmarks of severe COVID-19. If the virus is not constrained, this feedback loop results in a devastating inflammatory response called the cytokine storm (13) (**Figure 2**).

Natural killer (NK) cells, are among the first cells of the innate immunity system to respond to a pathogenic virus. Primed by type IFNs of APCs, the NK cells recognize antigens (Ag) independent of major histocompatibility molecules (MHC), which allows for a rapid reaction. NK cells possess a plethora of activating (e.g. NKG2D) and inhibitory (e.g. NKG2A) receptors. Macrophages and DCs, present foreign Ag to naïve CD4+ helper T cells (Th), and naïve CD8+ Cytotoxic T cells (CTLs) via MHC-II and MHC-I, respectively. By secreting stimulating factors including IL-2, IFN-γ, and tumor necrosis factor (TNF), Th1, it further stimulates CTLs, a major player against viral infections. Th2, governs the humoral aspect of adaptive immunity by stimulating B cells. Upon activation, B cells differentiate into memory B cells and plasma cells, releasing neutralizing poly-clonal IgM and then, long-lasting specific IgG (14). A previous study showed that memory T cells persist against SARS-CoV for up to four years after the first exposure (15). Another study reported the existence of memory T cells 6 years post-exposure to SARS-CoV, while specific SARS-CoV IgG was undetectable in the recovered patients (16). Lymphopenia, which is mostly a result of virus cytotoxicity and infiltration, as well as sequestration of lymphocytes in lungs and

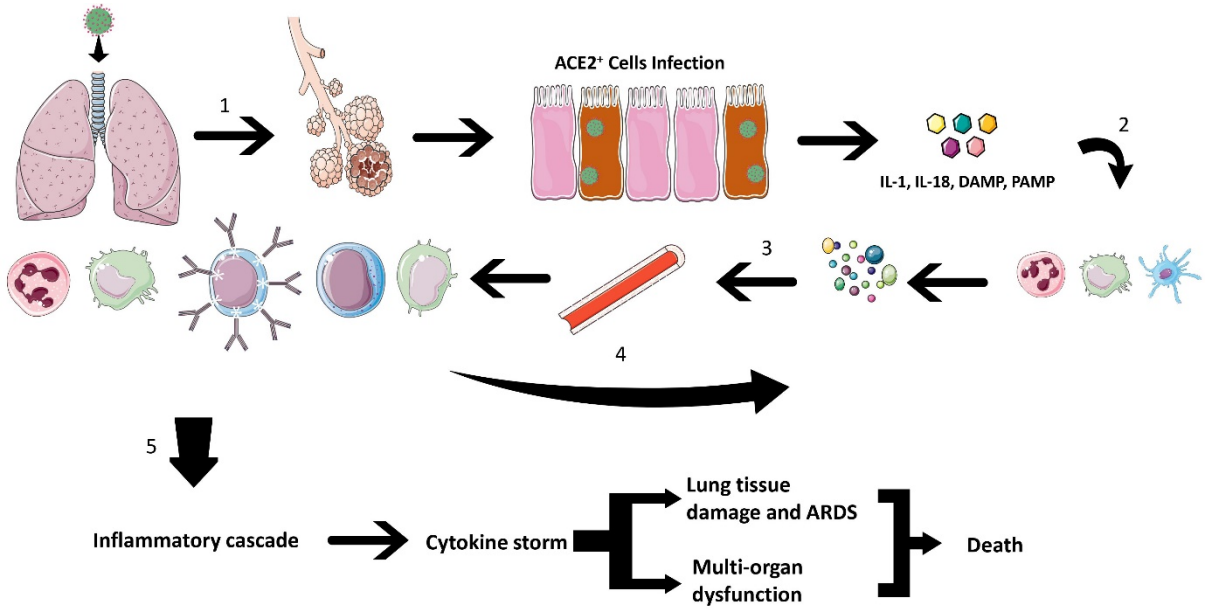

Figure 2. A schematic summarizing the immunopathogenesis of SARS-CoV-2 infection. (1) The virus enters the lung and proceeds to the lower the respiratory tract to invade ACE2+ pulmonary cells. After the pyroptosis of the infected cells, the damaged cells secrete the damage and pathogen-associated molecular patterns. (2) DAMPs are recognized by the resident immune cells, resulting in the secretion of inflammatory cytokines, such as MIP1, MCP-1, IL-6, and IL-10. The produced inflammatory cytokines recruit other immune cells from the neighboring blood vessels. (4) If the virus is not contained, the cycle of immune cell recruitment continues, which causes an excess infiltration of the immune cells into the lungs (5). The over activation of immune system and overproduction of inflammatory cytokines, results in cytokine storm, tissue damage in lungs and other ACE2 expressing tissues, ARDS and multiple organ failure and finally, leads to death.

other organs, is a common laboratory finding in COVID-19 patients. This is mostly due to low CD8+ T cell count and, to some extent, low CD4+ T cell, NK cell, and B cell counts. Also, T cell exhaustion is reported as another important, common symptom of COVID-19 patients, particularly in the intensive care unit's (ICU) patients. Studies have shown an overexpression of PD-1, CTLA-4, TIGIT, and Tim-3 T cell exhaustion markers in CD4+ and CD8+ T cell population of severe COVID-19 cases.

Such precise retort from the immune system, usually contains the virus with a local and limited immune response. However, if the virus is not eliminated, and spreads to the lower respiratory tract, the diffuse destruction of alveolar epithelial cells together with the infiltration and sequestration of the immune cells and their cytokines and toxins, leads to hypotension, coagulopathy, ARDS, and even death. Hypotension and vasodilation are due to systemic inflammatory responses, while coagulopathy is mostly attributed to pulmonary thrombotic microangiopathy (17).

Convalescent Plasma Therapy

Convalescent plasma (CP) therapy seeks to harness the already existing virus-specific antibodies in the serum of convalescent patients, to provide a rapid antibody response against the virus, since, it requires no activation of the immune system unlike vaccination. This method of therapy has been previously used to increase the survival rate of patients with serious infections such as SARS, MERS, pandemic influenza A, and Ebola virus disease (18,19). The specific anti-SARS-CoV-2 antibodies in the serum of recovered patients, can bind to the S protein of the virus. This results in the inability of the virus to attach to the ACE2 receptors, opsonization and phagocytosis, and complement activation (20). The serum concentration of immunoglobulin is highest in the convalescent stage of the disease and should be collected within 2 weeks after recovery for the antibodies to have a high titer (21). Not only CP provides patients with neutralizing antibodies, it also transfers other proteins, such as anti-inflammatory cytokines,

defensins, clotting factors, and natural antibodies, which may empower its immunomodulatory role (22).

A number of studies have demonstrated the feasibility of using CP therapy to treat the COVID-19 patients (23). Zhang *et al.* reported the recovery of four critically ill patients using supportive care and CP therapy (24). The results of a recent clinical trial (NCT04343261) showed that 63% of the COVID-19 patients who received CP with sufficient SARS-CoV-2 IgG, have recovered. Also, the patients who received CP therapy earlier in the course of the disease, had lower hospital mortality and hospitalization period (25). In another study, in five severely ill patients the ARDS resolved, following convalescent plasma infusion in tandem, along with antiviral therapy (26). Overall, CP therapy helps to minimize the clinical symptoms of the patients (e.g. cough, fever, pneumonia, oxygen saturation), decrease lung infiltration of immune cells and inflammatory indicators (C-reactive protein and IL-6), revert lymphopenia, reduce hospitalization, and lowers the viral load (27). Thus, CP transfusion is particularly beneficial to critical COVID-19 patients, especially in the earlier phases of the disease. This is mainly because immunoglobulins are more effective prophylactic agents than therapeutic (28). Other sources of plasma are also being investigated. A study is underway to utilize the anti-SARS-CoV-2 antibodies of hyperimmune equine serum after repeated immunization of the horses (NCT04610502). The limitations to CP therapy include procurement difficulty, transfusion-related adverse effects, anaphylactic shock, and pulmonary edema, disease transmission, ephemeral immunity, and non-specificity, which have prompted some companies to produce purified, high-concentration immunoglobulins (29).

Monoclonal Antibodies

Monoclonal antibodies (mAb) are designed to provide passive immunity against SARS-CoV-2, ameliorate the detrimental effects of hyperinflammatory responses, or boost the immune cells against the invading virus. This mode of therapy is specific and minimizes the adverse effects associated with the CP therapy, and is being extensively researched. The human 47D11 antibody, was the first anti-SARS-CoV-2 monoclonal antibody to be discovered. 47D11 specifically binds to the conserved epitope of $S1_B$ RBD of SARS-CoV-2 (30). There are currently at least 50 mAbs in development against SARS-CoV-2 (31).

Antibodies Against SARS-CoV-2 Spike Protein

As mentioned, S protein is crucial in the viral entry in both SARS-CoV and SARS-CoV-2. The amino acid sequence of S protein in SARS-CoV, has 77% similarity to that of SARS-CoV-2. This similarity rises to 89.8% in the S2 subunit of SARS-CoV-2, highlighting the fact that neutralizing antibodies previously directed against SARS-CoV, can be repurposed for COVID-19 (32). Still, testing various antibodies has shown different results. For instance, although the CR3022 human antibody interacts with epitopes other than RBDs of SARS-CoV-2, it has a higher affinity for SARS-CoV-2 (33). This is also the case for F26G19 and D12 mouse antibodies, but they are more inclined to bind to SARS-CoV RBDs (34). Other potential neutralizing antibodies such as 1G10, S309 1A9, 4B12, and 2B2 are currently being investigated (35). In general, anti-S mAbs are more suitable for the onset of infection before the virus' replication becomes uncontrollable.

Besides the previously existing antibodies, bioengineered, humanized antibodies against S protein are being enrolled in clinical trials. REGN-CoV2, a cocktail of casirivimab and imdevimab mAbs approved for emergency use authorization (EUA), stops the virus from binding to ACE2 receptor by blocking its non-overlapping epitopes of the S protein. REGN-CoV2 is approved for moderate non-hospitalized COVID-19 patients, or those at high risk of progressing to severe COVID-19 (31). In an ongoing analysis of 275 outpatients, REGN-CoV2 reduced the viral load, especially in patients with high viral load at the start of therapy and patients in whom an immune response was not started (36). Same as REGN-CoV2, bamlanivimab (LY-CoV555) is another anti-S protein mAb, EUA granted for non-hospitalized, mild to moderate COVID-19 patients who are at risk of developing severe symptoms. This was after the results of a

phase 2 trial reported a reduced viral load in 465 outpatients who received bamlanivimab (37). In a recent clinical trial, however, bamlanivimab monotherapy administration was not associated with a lower viral load in 533 non-hospitalized, mild to moderate patients (38).

Immunomodulatory Antibodies

Apart from neutralizing SARS-CoV-2, regulating the distressed immune environment caused by the over activation of immune cells is another target for mAbs. By modulating the immune response, the burden on organs caused by inflammation, can be contained. Immunomodulatory antibodies are developed to specifically target and inhibit the functions of inflammatory cytokines or their respective receptors. Immunomodulatory antibodies are best suited for severe cases in which side effects of the virus replication can be lethal (31).

IL-6 Inhibitors

As immunomodulatory agents, IL-6 mAbs are divided into anti-IL-6 receptors (e.g., sarilumab, tocilizumab) and anti-IL-6 mAbs (Siltuximab). Tocilizumab and sarilumab are humanized mAbs used as a treatment for inflammatory diseases, such as arthritis, and prevent the binding of IL-6 to its receptor. Early results from China showed that tocilizumab improved the outcome of the COVID-19 hospitalized patients (39). Multiple case reports have shown the ability of tocilizumab to alleviate clinical symptoms and the laboratory findings associated with cytokine storm in COVID-19 patients (39,40), and in a patients with multiple myeloma (41). Recently, The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) investigators, published the results of its clinical trial on critically ill ICU patients and demonstrated the efficacy and survival benefits of tocilizumab (8 mg/kg of body weight) (n=353) and sarilumab (400 mg/kg of body weight) (n=48) (42). The largest clinical trial on tocilizumab to date, was reported by the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group on hospitalized but not critical COVID-19 patients in UK. Depending on the weight, 2022 patients with systemic inflammation (C-reactive protein>75mg/L) and hypoxia (oxygen saturation<92%) were administered two doses of 400-800 mg of tocilizumab. Hospitalized patients who received tocilizumab, were more likely to be discharged within 28 days and experienced improved survival rate and other clinical outcomes (43). Sarilumab can be used alone or with tocilizumab to thwart inflammation. Sarilumab is not U.S. Food and Drug Administration (FDA)-approved for acute inflammations such as cytokine release syndrome associated with the chimeric antigen receptor (CAR) T cells (44). The results of the efficacy of sarilumab are controversial. Gremese *et al*. reported improved clinical outcome in 53 patients infused with 400 mg of sarilumab (45). An open-label cohort study of 56 critical COVID-19 patients, showed no significant clinical or mortality improvement following the sarilumab administration (400 mg) compared to a standard-of-care group (46). Also, in a recent double-blind trial, patients who received 400 mg (n=173) or 200 mg of sarilumab (n=159) experienced no significant clinical or survival improvement in comparison to the placebo group (n=84) (47).

Siltuximab is currently the only FDA-approved mAb specific for IL-6. The current utilization of siltuximab is for the idiopathic Castleman disease, and data on its efficacy in the context of COVID-19, is scarce (48). A prospective cohort study on 30 critical COVID-19 patients in Italy, administered the patients with two doses of siltuximab (11 mg/kg) and monitored them for 30 days (49). Only the risk of mortality was reported in this study, which was lower in the patients who have gone through siltuximab treatment.

IL-1 Receptor Antagonist

As an antagonist of the IL-1 receptor, anakinra inhibits the activity of IL-1α and IL-1β and is used as a therapeutic option for autoimmune disorders, such as rheumatoid arthritis (50). Multiple studies have shown decreased mortality as a result of anakinra administration. In a retrospective study, anakinra improved the clinical outcome of 22 severe patients (51). Such positive association was also reported in a prospective, open-label, interventional study on 69 patients, whom experienced a significant decrease in inflammatory cytokines after the

administration (52). In a retrospective cohort study, a high-dose of anakinra was correlated with a decreased level of serum CRP and improved the respiratory function (53). Anakinra is also capable of decreasing IL-6 levels and restoring the pro-inflammatory cytokine balance (54). It is also likely to decrease the need for invasive mechanical ventilation in the ICU patients, and the mortality of severe cases (55). However, one recent retrospective analysis of 57 patients, found no improvement in the survival outcome of patients receiving anakinra alone, thus, it makes further investigations more imperative (56).

Granulocyte-macrophage colony-stimulating Factor (GM-CSF) Inhibitors

An excessive amount of GM-CSF and trafficking of inflammatory myeloid cells to the lungs is directly correlated with severe COVID-19 progression, cytokine storm, and ARDS, making targeting GM-CSF function a potential treatment. Various studies have illustrated that targeting the GM-CSF, also alleviates other pro-inflammatory cytokines such as IL-6 (57). The first clinical use of lenzilumab was for 12 patients with risk factors of poor prognosis. Following three doses of 600 mg lenzilumab, a significant improvement was observed in oxygenation and the CRP and IL-6 levels. Also, in two days, the inflammatory myeloid cells were reduced with no treatment-related adverse effects (58). A case-cohort study of 12 critical COVID-19 patients, denoted faster improvements in clinical outcomes, reduced ARDS, and lower inflammatory markers (CRP and IL-6) (59). Other anti-GM-CSF mAbs include TJ003234, Mavrilimumab/KPL 30D, and Gimsilumab (KIN-190 N), among others (57).

Complement Inhibitors

Blocking the complement system, seems to be the recent trend in subsiding the inflammatory response in COVID-19 patients. The results of a study on 80 severely ill COVID-19 patients, have shown proof of principle for complement inhibition therapy using eculizumab, a C5a complement factor inhibitor (60). It seems that eculizumab administration can inhibit thrombotic microangiopathy (TMA) and subsequent acute kidney injury (AKI) associated with complement system over activation (61). The deposition of C5b-9 complement factors in renal tubules of COVID-19 patients is implicated in AKI (62). Care must be taken when suppressing the complement system and its downstream proteins, such as Membrane Attack Complex (MAC), since it might make patients susceptible to bacterial infections (63). Several other immunomodulatory mAbs in different phases of clinical trials are leronlimab (CCR5 antagonist), canakinumab (anti-IL-1β), cizanlizumab (anti-P-selectin), ravulizumab (anti-C5), bevacizumab (anti-VEGF), emapalumab (IFN-γ antagonist) (31).

Janus Kinase Inhibitors

Kinase inhibitors, such as janus kinase (JAK) inhibitors, are proposed as immunomodulatory treatments for COVID-19, since they prevent the phosphorylation of proteins, including the signal transducer and activator of transcription (STAT) proteins, that lead to inflammation. Additionally, JAK inhibitors can prevent viral entry by inhibiting AAK1, a kinase that facilitates clathrin-mediated endocytosis of SARS-CoV-2. Furthermore, JAK-dependent inhibition of ACE2 production is another favorable outcome of JAK inhibitors. Baricitinib is a prime example of a JAK inhibitor that meets these criteria (64). The use of baricitinib with anti-viral drugs, such as ritonavir, lopinavir, and ramsudavir, is suggested to ameliorate immune system hyperinflammatory response and ARDS. One important target for fedratinib JAK inhibitor is Th17. The inflammatory cytokines of Th17 are an important driving force of cytokine storm and the overall pathophysiology of COVID-19. These cells require JAK signaling to differentiate and exert their effector functions (65). A case series report of ruxolitinib JAK inhibitor, showed a significant reduction of inflammation score and improvement of clinical and radiological outcomes (66).

IFN-based Immunotherapy

The large family of type 1 interferons, such as IFN-α and IFN-β, are central in driving anti-viral defense and organizing the immune responses by inhibiting the virus's replication in infected cells, boosting antigen presentation, and stimulating the adaptive immune response (67). In China, IFN

therapy with anti-viral drugs, such as ribavirin, is considered as a recommended treatment option (68). Early administration of IFN-α-2b, is associated with diminished viral loads, higher serum anti-SARS-CoV-2 antibody, and improved clinical responses (69). IFN therapy is usually used in combination with other therapies. IFN-α-2b in combination with CP therapy, and anti-viral drugs (24), and IFN-α-1b with CP therapy, anti-viral drugs, and methylprednisolone (26), have shown efficacy in improving the clinical outcomes of severe COVID-19 cases. IFN has also been efficacious in combination with tocilizumab and anti-viral drugs (39) and human umbilical cord mesenchymal stem cells (hUCMSCs) (70). Clinical trials are ongoing to investigate the efficiency of IFN-α, -β, and –λ as dual therapy with other conventional or novel therapies (71).

Cell Therapy

Cell therapy, also known as adoptive cell therapy (ACT), is a form of adaptive immunotherapy that harnesses the potential of immune cells to fend off the disease. Cell therapy, although mostly investigated in the field of cancer therapy, has shown promise, as a therapeutic approach, in viral infections such as HIV (72) and persistent viral infections in stem cell transplantation patients (73). Considering the urgency of COVID-19, scientists and physicians are trying to apply their ACT knowledge to the context of this disease.

Natural Killer Therapy

NK cells are one of the most prominent cells of innate immunity in the fight against viral infections. This is especially due to the rapid response of NK cells, which is indebted to their independence from MHC molecules to recognize invading pathogens. Adoptively transferring the NK cells, is a viable strategy. NK cells can be used as monotherapy or combination therapy with memory T cells of convalescent donors (NCT04578210), as well as conventional therapy (NCT04280224). One trial is trying to use "off-the-shelf" NK cells derived from induced pluripotent stem cells (iPSCs), named FT516, to investigate its efficacy in COVID-19 patients. Other sources of cells from which NK cells can be derived, include human placental CD34+ stem cells (NCT04365101) and CD34+ hematopoietic stem cells (NCT04900454). Potentially, the NKG2A inhibitory receptor of the NK cells, can also be inhibited to boost the cell's function, since NKG2A is reportedly upregulated in COVID-19 patients and is considered as an exhaustion marker (74).

Genetically engineered constructs known as chimeric antigen receptors (CARs), have revolutionized the field of cancer immunotherapy since their introduction. These constructs express on the cells in which they are transduced and can recognize specifically designated antigens. Whether this antigen is associated with a tumor cell or a virus, such as SARS-CoV-2, CARs allows the cell its mounted on to recognize and attack the antigen in an MHC-independent manner (75). In a phase I/II trial, CAR-expressing the NK cells are designed to target the S protein and NKG2DL of the virus-infected cells, using their surface ACE2 and NKG2D proteins. The exosome secreted from cell's culture in the media, can also be used as a therapy. These exosomes, which are released upon CAR-NK cell expansion, are recently shown to have high concentrations of the cytotoxic proteins (76).

T Cell Therapy

T-lymphocytes are the pillars of the cellular immunity and are crucial in the viral invasion; lymphopenia and exhausted T cells are usually associated with poor outcomes in COVID-19 patients. After convalescence, CD8+ T cell count and CD4/CD8 T cell ratio reverts to normal. Virus-specific T cells (VSTs) are shown to proficiently target SARS-CoV-2 and are persistent for a few weeks after convalescence, making the use of VSTs a viable strategy for COVID-19 patients (77). Some preclinical studies have attempted to isolate the VSTs from convalescent patients, and expand them in ex vivo culture conditions using the good-manufacturing practice (GMP) (78–81). The function of the isolated VSTs, was determined by their response to the virus and secreting IFN-γ, and their phenotype shifted to memory cells after two weeks, but the number of circulating VSTs dropped significantly after two months of convalescence (77). In an indirect approach, expanded VSTs can release exosomes that are rich in IFN. The exosomes lack MHC proteins, making the arduous process of matching

HLA redundant (NCT04389385).

These are studies that are pushing forward the use of other subsets of T cells instead of polyclonal T cells. As a small proportion of T cells, γδ T cells, exhibit a wide range of antiviral activity and demonstrate traits related to both innate and adaptive immunity. Although γδ T cells' small numbers are not in favor of being used as a therapy, trials are investigating their feasibility against COVID-19 (NCT04834128). Previous success with transferring regulatory T cells (Tregs) in autoimmune and inflammatory disorders (82), has prompted the use of these cells to alleviate the hyperinflammatory response in severe cases (NCT04468971). In a case report study, the infusion of two severe COVID-19 patients with cord blood-derived regulatory T cells, resulted in a reduced level of IL-6 and TNF-α cytokines (83).

DC Therapy

DCs exert their function either directly by secreting cytokines, including IL-6, IP-10, and MCP-1, or indirectly via type I IFNs, to stimulate NK cells or act as APC. Despite of the importance of DCs in kick-starting the adaptive immunity, one strategy aims to direct the DCs against SARS-CoV-2 by loading such cells with S protein in vitro (NCT04386252). Secondly, DCs vaccine, conventionally used in cancer treatment, are being explored in the fight against COVID-19. In a trial, DCs are transfected using a lentiviral vector (NHP/TYF), which carries genes for SARS-CoV-2 proteins and immunomodulatory cytokines (NCT04276896). Lastly, a stratagem is to hinder the activation of type I DCs, whose production of cytokines is a cause for ARDS. Although the DC vaccines have failed to elicit robust immunity for HIV, HCV, and CMV, the current trials will illustrate whether the DC vaccines are efficacious for SARS-CoV-2 or not (84–86).

Conclusion

Antiviral drugs and vaccines are effective in improving the clinical manifestations of COVID-19, reducing the hospitalization period, and breaking the transmission cycle of SARS-CoV-2. Nevertheless, a standard cure or treatment is still lacking. Other potential treatments must be scrutinized as either a definitive treatment against SARS-CoV-2 or as palliative treatment for the virus' side effects, including ARDS and cytokine storm. Accordingly, immunotherapeutic approaches that were previously utilized in the context of other maladies, such as cancer and chronic viral infections, are being trialed. These cellular/acellular immunotherapeutic approaches could be administered alone or be combined with other antiviral therapies, depending on the severity or stage of the disease. The current and future trials will determine the efficacy of immunotherapeutic methods, and their feasibility will be determined based on many criteria, such as costs, rapidity, toxicity, availability, and effectiveness.

Conflict of interest

The authors report no conflict of interest.

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References

1. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science [Internet]. 2013;342(6165):1432–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24357284
2. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine and Growth Factor Rev. 2020;(53):66–70.
3. Sonani B, Aslam F, Goyal A, Patel J, Bansal P. COVID-19 vaccination in immunocompromised patients. Clin Rheumatol. 2021;40(2):797–8.
4. Iqbal Yatoo M, Hamid Z, Parray OR, Wani AH, Ul Haq A, Saxena A, et al. COVID-19 - Recent advancements in identifying novel vaccine candidates and current status of upcoming SARS-CoV-2 vaccines. Hum Vaccin Immunother. 2020;16:2891–904.
5. Masoomikarimi M, Garmabi B, Alizadeh J, Kazemi E, Azari Jafari A, Mirmoeeni S, et al. Advances in immunotherapy for COVID-19: A comprehensive review. Int Immunopharmacol. 2021;93:107409-23.
6. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3.
7. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function,

and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281–292.e6.
8. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020;9(1):45-52.
9. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med. 2020;172(9):577–82.
10. Liu Y, Mao B, Liang S, Yang JW, Lu HW, Chai YH, et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J. 2020;55(5):2001112-5.
11. Chu H, Chan JF-W, Yuen TT-T, Shuai H, Yuan S, Wang Y, et al. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. Lancet Microbe. 2020;1(1):e14–23.
12. Mortaz E, Tabarsi P, Varahram M, Folkerts G, Adcock IM. The Immune Response and Immunopathology of COVID-19. Front Immunol. 2020;11:2037-46.
13. Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: Implications for SARS. Vol. 5, Nat Rev Immunol. 2005;5(12):917–27.
14. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102–8.
15. Fan YY, Huang ZT, Li L, Wu MH, Yu T, Koup RA, et al. Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. Arch Virol. 2009;154(7):1093–9.
16. Tang F, Quan Y, Xin Z-T, Wrammert J, Ma M-J, Lv H, et al. Lack of Peripheral Memory B Cell Responses in Recovered Patients with Severe Acute Respiratory Syndrome: A Six-Year Follow-Up Study. J Immunol. 2011;186(12):7264–8.
17. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J. 2021;97(1147):312–20.
18. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Vol. 20, Lancet Infect Dis. 2020;20(4):398–400.
19. Cheng Y, Wong R, Soo YOY, Wong WS, Lee CK, Ng MHL, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24(1):44–6.
20. Zhou G, Zhao Q. Perspectives on therapeutic neutralizing antibodies against the novel coronavirus sars-cov-2. Int J Biol Sci. 2020:16(10):1718–23.
21. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020;55(5): 105955-67.
22. Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in Covid-19: Possible mechanisms of action. Autoimmun Rev. 2020;19:102554.
23. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020;117(17):9490–6.
24. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. Chest. 2020;158(1):e9–13.
25. Ibrahim D, Dulipsingh L, Zapatka L, Eadie R, Crowell R, Williams K, et al. Factors Associated with Good Patient Outcomes Following Convalescent Plasma in COVID-19: A Prospective Phase II Clinical Trial. Infect Dis Ther. 2020;9(4):913–26.
26. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. JAMA - J Am Med Assoc. 2020;323(16):1582–9.
27. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two covid-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci. 2020;35(14):e149.
28. Iqbal Yatoo M, Hamid Z, Rather I, Nazir QUA, Bhat RA, Ul Haq A, et al. Immunotherapies and immunomodulatory approaches in clinical trials - a mini review. Hum Vaccines Immunother. 2021;17(7):1897–909.
29. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130(40):1545–8.
30. Wang C, Li W, Drabek D, Okba NMA, van Haperen R, Osterhaus ADME, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. Nat Commun. 2020;11(1):2251-68.
31. Deb P, Molla MMA, Saif-Ur-Rahman KM. An update to monoclonal antibody as therapeutic option against COVID-19. Biosaf Health. 2021;35(2):87–91.
32. Xia S, Liu M, Wang C, Xu W, Lan Q, Feng S, et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike

protein that harbors a high capacity to mediate membrane fusion. Cell Res. 2020;30(4):343–55.
33. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. 2020;9(1):382–5.
34. Tamina Park, Sang-Yeop Lee, Seil Kim, Mi Jeong Kim, Hong Gi Kim, Sangmi Jun, Seung Il Kim, Bum Tae Kim, Edmond Changkyun Park DP. Spike protein binding prediction with neutralizing antibodies of SARS-CoV-2. bioRxiv. 2021; Available from: https://doi.org/10.1101/2020.02.22.951178
35. Pinto D, Park YJ, Beltramello M, Walls AC, Tortorici MA, Bianchi S, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature. 2020;583(7815):290–5.
36. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2021;384(3):238–51.
37. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2021;384(3):229–37.
38. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA - J Am Med Assoc. 2021;325(7):632–44.
39. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970–5.
40. Michot JM, Albiges L, Chaput N, Saada V, Pommeret F, Griscelli F, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann Oncol. 2020;31(7):961–4.
41. Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020;4(7):1307–10.
42. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491–502.
43. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45.
44. Khiali S, Rezagholizadeh A, Entezari-Maleki T. A comprehensive review on sarilumab in COVID-19. Expert Opin Biol Ther 2021;21(5):615–26.
45. Gremese E, Cingolani A, Bosello SL, Alivernini S, Tolusso B, Perniola S, et al. Sarilumab use in severe SARS-CoV-2 pneumonia. EClinicalMedicine. 2020;27:69-78.
46. Della-Torre E, Campochiaro C, Cavalli G, De Luca G, Napolitano A, La Marca S, et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: An open-label cohort study. Ann Rheum Dis. 2020;79(10):1277–85.
47. Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(5):522–32.
48. Gritti G, Raimondi F, Bottazzi B, Ripamonti D, Riva I, Landi F, et al. Siltuximab downregulates interleukin-8 and pentraxin 3 to improve ventilatory status and survival in severe COVID-19. Leukemia. 2021;35:2710-14.
49. Palanques-Pastor T, López-Briz E, Poveda Andrés JL. Involvement of interleukin 6 in SARS-CoV-2 infection: Siltuximab as a therapeutic option against COVID-19. Eur J Hosp Pharm. 2020;27(5):297–8.
50. Furst DE. Anakinra: Review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004;26(12):1960–75.
51. Cauchois R, Koubi M, Delarbre D, Manet C, Carvelli J, Blasco VB, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A. 2020;117(32):18951–3.
52. Balkhair A, Al-Zakwani I, Al Busaidi M, Al-Khirbash A, Al Mubaihsi S, BaTaher H, et al. Anakinra in hospitalized patients with severe COVID-19 pneumonia requiring oxygen therapy: Results of a prospective, open-label, interventional study. Int J Infect Dis. 2021;103:288–96.
53. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325–31.
54. Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N, et al. An open label trial of anakinra to prevent respiratory failure in covid-19. Elife. 2021;10:66125-34.
55. Huet T, Beaussier H, Voisin O, Jouveshomme S,

Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020;2(7):e393–400.
56. Narain S, Stefanov DG, Chau AS, Weber AG, Marder G, Kaplan B, et al. Comparative Survival Analysis of Immunomodulatory Therapy for Coronavirus Disease 2019 Cytokine Storm. Chest. 2021;159(3):933–48.
57. Lang FM, Lee KMC, Teijaro JR, Becher B, Hamilton JA. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. Nat Rev Immunol. 2020;20(8):507–14.
58. Temesgen Z, Assi M, Vergidis P, Rizza S, Bauer P, Pickering B, et al. First Clinical Use of Lenzilumab to Neutralize GM-CSF in Patients with Severe and Critical COVID-19 Pneumonia. medRxiv Prepr Serv Heal Sci. 2020;
59. Temesgen Z, Assi M, Shweta FNU, Vergidis P, Rizza SA, Bauer PR, et al. GM-CSF Neutralization With Lenzilumab in Severe COVID-19 Pneumonia: A Case-Cohort Study. Mayo Clin Proc. 2020;95(11):2382–94.
60. Annane D, Heming N, Grimaldi-Bensouda L, Frémeaux-Bacchi V, Vigan M, Roux AL, et al. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: A proof-of-concept study. EClinicalMedicine. 2020;28:100590-99.
61. Mahajan R, Lipton M, Broglie L, Jain NG, Uy NS. Eculizumab treatment for renal failure in a pediatric patient with COVID-19. J Nephrol. 2020;33(6):1373–6.
62. Diao B, Wang C, Wang R, Feng Z, Zhang J, Yang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. Nat Commun. 2021;12(1):2506-17.
63. Vlaar APJ, de Bruin S, Busch M, Timmermans SAMEG, van Zeggeren IE, Koning R, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. Lancet Rheumatol. 2020;2(12):e764–73.
64. Spinelli FR, Conti F, Gadina M. HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. Sci Immunol. 2020;5(47): eabc5367.
65. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect. 2020;53(3):368–70.
66. La Rosée F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia. 2020;34(7):1805–15.
67. Murira A, Lamarre A. Type-I interferon responses: From friend to foe in the battle against chronic viral infection. Front Immunol. 2016;7:609-21.
68. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58–60.
69. Wang N, Zhan Y, Zhu L, Hou Z, Liu F, Song P, et al. Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients. Cell Host Microbe. 2020;28(3):455–464. e2.
70. Liang B, Chen J, Li T, Wu H, Yang W, Li Y, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. Medicine (Baltimore). 2020;99(31):e21429.
71. Mansourabadi AH, Sadeghalvad M, Mohammadi-Motlagh HR, Rezaei N. The immune system as a target for therapy of SARS-CoV-2: A systematic review of the current immunotherapies for COVID-19. Vol. 258, Life Sci. 2020;258:118185-98.
72. Qi J, Ding C, Jiang X, Gao Y. Advances in Developing CAR T-Cell Therapy for HIV Cure. Vol. 11, Front Immunol. 2020;11:361-379.
73. Ottaviano G, Chiesa R, Feuchtinger T, Vickers M, Dickinson A, Gennery A, et al. Adoptive T Cell Therapy Strategies for Viral Infections in Patients Receiving Haematopoietic Stem Cell Transplantation. Cells. 2019;8(1):47-54.
74. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020;17(5):533–5.
75. Mohanty R, Chowdhury CR, Arega S, Sen P, Ganguly P, Ganguly N. CAR T cell therapy: A new era for cancer treatment (Review). Oncol Rep. 2019;42(6):2183–95.
76. Fu W, Lei C, Liu S, Cui Y, Wang C, Qian K, et al. CAR exosomes derived from effector CAR-T cells have potent antitumour effects and low toxicity. Nat Commun. 2019;10(1):4355-63.
77. Cooper RS, Fraser AR, Smith L, Burgoyne P, Imlach SN, Jarvis LM, et al. Rapid GMP-Compliant Expansion of SARS-CoV-2–Specific T Cells From Convalescent Donors for Use as an Allogeneic Cell Therapy for COVID-19. Front Immunol. 2021;11: 598402.
78. Keller MD, Harris KM, Jensen-Wachspress MA, Kankate V V., Lang H, Lazarski CA, et al. SARS-CoV-2–specific T cells are rapidly expanded for

therapeutic use and target conserved regions of the membrane protein. Blood. 2020;136(25):2905–17.
79. Leung W, Soh TG, Linn YC, Low JG, Loh J, Chan M, et al. Rapid production of clinical-grade SARS-CoV-2 specific T cells. Adv CELL GENE Ther. 2020;3(4):1-8.
80. Leung W, Soh TG, Linn YC, Low JG-H, Loh J, Chan M, et al. SUCCESSFUL MANUFACTURING OF CLINICAL-GRADE SARS-CoV-2 SPECIFIC T CELLS FOR ADOPTIVE CELL THERAPY. medRxiv [Internet]. 2020 Jan 1;2020.04.24.20077487. Available from: http://medrxiv.org/content/early/2020/04/30/2020.04.24.20077487.abstract
81. Ferreras C, Pascual-Miguel B, Mestre-Durán C, Navarro-Zapata A, Clares-Villa L, Martín-Cortázar C, et al. SARS-CoV-2-Specific Memory T Lymphocytes From COVID-19 Convalescent Donors: Identification, Biobanking, and Large-Scale Production for Adoptive Cell Therapy. Front Cell Dev Biol. 2021;(9):1-12.
82. Romano M, Fanelli G, Albany CJ, Giganti G, Lombardi G. Past, present, and future of regulatory T cell therapy in transplantation and autoimmunity. Front Immunol. 2019;10:1-14.
83. Gladstone DE, Kim BS, Mooney K, Karaba AH, D'Alessio FR. Regulatory T Cells for Treating Patients With COVID-19 and Acute Respiratory Distress Syndrome: Two Case Reports. Ann Intern Med. 2020;173(10):852–3.
84. Van Craenenbroeck AH, Smits ELJ, Anguille S, Van De Velde A, Stein B, Braeckman T, et al. Induction of cytomegalovirus-specific T cell responses in healthy volunteers and allogeneic stem cell recipients using vaccination with messenger RNA-transfected dendritic cells. Transplantation. 2015;99(1):120–7.
85. da Silva LT, Santillo BT, de Almeida A, Duarte AJ da S, Oshiro TM. Using Dendritic Cell-Based Immunotherapy to Treat HIV: How Can This Strategy be Improved? Front Immunol. 2018;9:2993.
86. Zhou Y, Zhang Y, Yao Z, Moorman JP, Jia Z. Dendritic cell-based immunity and vaccination against hepatitis C virus infection. Immunology. 2012;136(4):385–96.